other fee occasioned by this paper, or credit any overpayment in such fees, to Deposit Account No. 50-0320.

REMARKS

The Office Action required restriction to one of the following Groups under 35 U.S.C. §121:

Group I: Claims 1-33, drawn to inteins.

Group II: Claims 34-38 and 67-72, drawn to DNA.

Group III: Claims 39-47, drawn to methods of producing a protein enzymatically.

Group IV: Claims 48-49, drawn to methods of purification.

Group V: Claims 50-52, drawn to methods of preparing an intein comprising random mutagenesis.

Group VI: Claims 53-60, drawn to methods of screening for intein cleavage activity.

Group VII: Claims61-66, drawn to methods of determining amino acid residues in an intein that play a role in cleavage activity

It is respectfully requested that the restriction requirement be reconsidered and withdrawn and that there be search, examination and prosecution of all of the claimed subject matter, for the reasons provided below.

Under 35 U.S.C. § 121, "two or more independent and distinct inventions ... in one application may... be restricted to one of the inventions." Inventions are "independent" if there is no distinct relationship between two or more subjects disclosed" (MPEP § 802.01). The term "distinct" means that "two or more subjects as disclosed are related ... but are capable of separate manufacture, use or sale as claimed, and are patentable (novel and unobvious) over each other (MPEP § 802.01, July 1988) (emphasis is original). However, even with patentably distinct inventions, restriction is not required unless one of the following reasons appear (MPEP § 808.02):

1. Separate classification;
2. Separate status in the art; or
3. Different field of search.

Under Patent Office examining procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP § 803) (emphasis added).

Groups I to VII designated by the Office Action fail to warrant separate examination and search. The present claims represent a web of knowledge and continuity of effort that merits examination in a single application.

Enforcing the present restriction requirement would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO, as well as extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional or continuing applications filed). Restriction has not been shown to be proper, especially since the requisite showing of serious burden has not been made in the Office Action and there are relationships between the claims of all seven Groups. Indeed, the search and examination of each Group is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of the entire application can be made without undue burden on the Examiner.

All of the preceding mitigate against restriction. Accordingly, it is respectfully requested that the restriction requirement be reconsidered and withdrawn, in view of there clearly being no serious or undue burden in searching and examining all of the Groups I to VII.

In the event that the request for withdrawal of the present restriction requirement is denied, it is respectfully requested that, at the very least, the restriction requirement be re-drawn, such that the claims of Groups I and II are re-joined into a single group (and examined as the presently elected Group), the claims of Groups III and IV are re-joined into a single group, and the claims of Groups V, VI, and VII be rejoined into a single group, for the reasons provided as follows.

The elected Group (i.e., Group I) is directed to intein proteins and polypeptides. Group II is directed to the DNA sequences that encode inteins. The Office Action asserts that restriction between Group I and II is justified because polypeptides and DNA are products with different

structures and biological properties. However, those of skill in the art accept that polypeptides and the DNA that encodes them are inextricably linked in the practice of all biotechnological inventions. Thus, most of the literature (including patents) in the field of biotechnology, including in the field of inteins, describes both polypeptides and the DNA sequences that encode them together and in relation to one another. Therefore, the search and examination of Groups I and II is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of both Groups can be made without undue burden on the Examiner.

Furthermore, a search of the claims of Group I directed to polypeptides will, most likely, also require a search of the DNA sequences encoding them. For example, claim 9 is directed to a mutant intein polypeptide, and claim 14 is directed to an intein polypetide having its endonuclease domain deleted. It is accepted in the art that the most efficient way to determine whether or not a given polypeptide is mutated or has a domain deleted is to sequence the DNA encoding that polypetide. Restriction between Groups I and II has thus been shown not to be proper because a separate search and examination of the claims of Groups I and II would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO. Therefore, re-joinder of the claims of Groups I and II is respectfully requested.

The Office Action states that Group III claims are drawn to methods of producing a protein enzymatically, while Group IV claims are directed to methods of purification. The Office Action asserts that restriction between Group III and IV is justified because producing and purifying a protein a protein require different biological reagents and parameters. However, these two groups are inter-related. All of the claims of Group IV include the step of "subjecting the intein to cleavage conditions", as do the claims of Group III. Therefore, the search and examination of Groups III and IV is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of both Groups can be made without undue burden on the Examiner. Furthermore, the USPTO has previously granted claims directed to both cleavage and purification of intein-containing proteins (see U.S, Patent 5,834,247). Thus, it is submitted that restriction between Groups III and IV is not proper, and that a separate search and examination of the claims of Groups III and IV would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO. Therefore, re-joinder of the claims of Groups III and IV is respectfully requested.

The Office Action states that Group V claims are drawn to methods of preparing an intein comprising random mutagenesis, Group VI claims are drawn to methods of screening for intein cleavage activity, and Group VII claims are drawn to methods of determining amino acid residues in an intein hat play a role in cleavage activity. The Office Action asserts that restriction between Group V, VI and VII is justified because random mutagenesis, screening for intein cleavage, and determing amino acid residues involved in cleavage, require different biological reagents and parameters. However, the claims in each of these groups are inter-related and depend on one another, such that the search and examination of Groups V, VI and VII is likely to be co-extensive. It is understood in the art that an inherent part of "screening" for proteins with a desired function is the provision of a mixed or random pool of proteins to provide the starting point for screening. The generation or provision of a starting pool (or library) of inteins by random mutagenesis is an integral part of the screening process. Thus, claim 53 (in Group VI) drawn to a method of screening, recites the step of "subjecting the intein DNA to random mutagenesis". Likewise, the methods of claim 61-66 (Group VII) drawn to methods of determining amino acid residues in an intein that play a role in cleavage activity are inextricably linked to the claims of Groups V and VI. In order to determine which amino acids in a given protein play a role in a given function or activity, it is usual to test or "screen" the function of multiple mutated proteins. Thus, claim 61 (Group VII) drawn to methods of determining amino acids involved in cleavage activity comprises the steps of "changing the amino acids in an intein" (i.e. mutagenesis) and "selecting" for reduced or elevated cleavage activity (i.e. screening). Furthermore, claim 63, also in groups VII, recites the method of changing the amino acids in an intein that is random mutagenesis.

Thus, the processes of random mutagenesis, screening for polypeptides with altered activities, and determining amino acid residues involved in given activities, are closely related and interdependent processes that are frequently described together in the literature. Therefore, the search and examination of Groups V, VI and VII is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of both Groups can be made without undue burden on the Examiner. Thus, it is submitted that restriction between Groups V, VI, and VII is not proper, and that a separate search and examination of the claims of Groups III and IV would result in inefficiencies and unnecessary expenditures by both the

Applicants and the PTO. Therefore, re-joinder of the claims of Groups V, VI, and VII is respectfully requested.

CONCLUSION

In view of the remarks herein, reconsideration and withdrawal, or re-drawing of the Restriction Requirement, and early and favorable examination on the merits of all of the claimed subject matter, is earnestly solicited.

Respectfully submitted,

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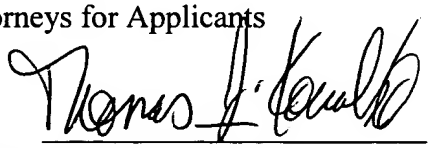
By: 

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